

WHAT IS CLAIMED IS:

1. An apparatus for growing cells comprising
at least one bioreactor for cell culture,
at least one vessel for culture medium,
means for circulating culture medium and/or cell culture, whereby the bioreactor and
vessel are in fluid communication, and
at least one means for delivery of oxygen.
2. The apparatus of claim 1 wherein the means for delivery of oxygen comprises a
hollow fiber filter oxygenator.
3. The apparatus of claim 1 wherein the means for delivery of oxygen comprises
means for in-line sparging.
4. The apparatus of claim 1 wherein the means for delivery of oxygen comprises
means for delivery of at least one oxygen-containing compound that releases dissolved oxygen
into cell culture.
5. The apparatus of claim 1 wherein the means for delivery of oxygen is positioned
upstream of input of circulating cell culture returning to the bioreactor.
6. The apparatus of claim 1 wherein the bioreactor and/or the vessel are stirred.
7. The apparatus of claim 1 wherein the means for delivery of oxygen provides an
average dissolved oxygen concentration of about 60%.
8. An apparatus for growing cells comprising
a bioreactor for cell culture,
a vessel for culture medium,
means for circulating cell culture,
means for circulating culture medium,
dialysis means in fluid communication with the bioreactor and the vessel,
whereby
there is
a first, cell culture, loop between the bioreactor and the dialysis means,
and
a second, media replenishment, loop between the vessel and the
bioreactor,

and in operation dialysis between the culture medium and the cell culture.

9. The apparatus of claim 8 wherein the dialysis means comprises at least one semi-permeable membrane.
10. The apparatus of claim 9 wherein the semi-permeable membrane comprises at least one hollow fiber filter.
11. The apparatus of claim 8 further comprising:
at least one means for delivery of oxygen into the cell culture loop.
12. The apparatus of claim 11 wherein the means for delivery of oxygen comprises a hollow fiber filter oxygenator.
13. The apparatus of claim 11 wherein the means for delivery of oxygen comprises means for in-line sparging.
14. The apparatus of claim 11 wherein the means for delivery of oxygen comprises means for delivery of at least one oxygen-containing compound that releases dissolved oxygen into cell culture.
15. The apparatus of claim 11 wherein the means for delivery of oxygen is positioned upstream of input of circulating cell culture returning to the bioreactor.
16. The apparatus of claim 8 or 11 wherein the bioreactor and/or the vessel are stirred.
17. The apparatus of claim 11 wherein the means for delivery of oxygen provides an average dissolved oxygen concentration of about 60%.
18. The apparatus of claim 11 wherein the means for delivery of oxygen provides an average dissolved oxygen concentration of greater than about 40%.
19. The apparatus of claim 18 wherein the means for deliver of oxygen provides an average dissolved oxygen concentration between about 30% and 90% or between about 40% and about 80% or between about 50% and 70%.
20. The apparatus of claim 11 further comprising:
means for measuring physical and/or chemical parameter(s) of the cell culture and/or the culture medium.
21. The apparatus of claim 20 wherein the means for measuring comprises means for measuring dissolved oxygen concentration.

22. The apparatus of claim 20 wherein the means for measuring comprises means for measuring pH.
23. The apparatus of claim 20 wherein the means for measuring comprises means for measuring temperature.
24. The apparatus of claim 20 wherein the means for measuring comprises means for measuring pH and means for measuring dissolved oxygen.
25. The apparatus of claim 20 wherein the means for measuring comprises means for measuring cell density or amount of cells.
26. The apparatus of claim 20 further comprising means for adjusting physical and/or chemical parameter(s) of the cell culture and/or the culture medium in response to data from the measuring means.
27. The apparatus of claim 26 wherein the adjusting means comprises means to adjust temperature.
28. The apparatus of claim 26 wherein the adjusting means comprises means for adjusting pH.
29. The apparatus of claim 26 wherein the adjusting means comprises means for adjusting dissolved oxygen concentration.
30. The apparatus of claim 26 wherein the adjusting means comprises means for adjusting dissolved carbon dioxide concentration.
31. The apparatus of claim 24 further comprising means for adjusting physical and/or chemical parameter(s) of the cell culture and/or the culture medium in response to data from the measuring means.
32. The apparatus of claim 31 wherein the adjusting means comprises means to adjust temperature.
33. The apparatus of claim 32 wherein the adjusting means comprises means for adjusting pH.
34. The apparatus of claim 32 wherein the adjusting means comprises means for adjusting dissolved oxygen concentration.
35. The apparatus of claim 32 wherein the adjusting means comprises means for adjusting dissolved carbon dioxide concentration.

36. The apparatus of claim 32 wherein the adjusting means comprises means for adding a vector in response to a cell density or cell amount measurement.

37. The apparatus of claim 32 wherein the adjusting means comprises means for adjusting dissolved oxygen and means for adjusting dissolved carbon dioxide, whereby in response to pH measurement(s), dissolved carbon dioxide levels are adjusted.

38. The apparatus of claim 37 wherein in response to dissolved oxygen measurement(s), dissolved oxygen levels are adjusted.

39. The apparatus of claim 38 wherein pH is set to a desired level and carbon dioxide is adjusted when pH varies from the desired level, whereby the dissolved oxygen measurement varies periodically as a function of time.

40. The apparatus of claim 39 wherein the dissolved oxygen measurement varies from 30% to 90% or from 40% to 80% or from 50% to 70%; or, the dissolved oxygen measurement averages about 60%.

41. The apparatus of claim 40 wherein the dissolved oxygen measurement varies from high value to low value over about 10 to about 30 minutes or over about 20 minutes.

42. The apparatus of claim 39 wherein a plot of the dissolved oxygen measurement as a function of time comprises a sin wave.

43. A method for growing cells comprising culturing cells in at least one bioreactor whereby there is a cell culture, supplying medium in at least one vessel whereby there is culture medium, circulating culture medium and/or cell culture, whereby the bioreactor and vessel are in fluid communication and the cell culture and/or culture medium are in circulation, and delivering oxygen to the cell culture and/or culture medium.

44. The method of claim 43 wherein the delivering of oxygen is by means for delivery of oxygen comprising a hollow fiber filter oxygenator.

45. The method of claim 43 wherein the delivering of oxygen is by means for delivery of oxygen comprising means for in-line sparging.

46. The method of claim 43 wherein the delivering of oxygen is by delivery of at least one oxygen-containing compound that releases dissolved oxygen into cell culture.

47. The method of claim 43 wherein the delivering of oxygen is upstream of input of circulating cell culture returning to the bioreactor.

48. The method of claim 43 further comprising stirring the cell culture or the culture medium or both the cell culture and the culture medium.

49. The method of claim 43 wherein the delivering of oxygen provides an average dissolved oxygen concentration of about 60%.

50. A method for growing cells comprising culturing cells in a bioreactor whereby there is a cell culture, supplying culture medium in a vessel where by there is culture medium, circulating the cell culture through a dialysis means, circulating culture medium through the dialysis means, wherein the dialysis means is in fluid communication with the bioreactor and the vessel, whereby there is a first, cell culture, loop between the bioreactor and the dialysis means, and a second, media replenishment, loop between the vessel and the bioreactor, and performing dialysis between the culture medium and the cell culture.

51. The method of claim 50 wherein the dialysis means comprises at least one semi-permeable membrane.

52. The method of claim 51 wherein the semi-permeable membrane comprises at least one hollow fiber filter.

53. The method of claim 50 further comprising: delivering oxygen into the cell culture loop.

54. The method of claim 53 wherein the delivering of oxygen is by means for delivery of oxygen comprising a hollow fiber filter oxygenator.

55. The method of claim 53 wherein the delivering of oxygen is by means for delivery of oxygen comprising means for in-line sparging.

56. The method of claim 53 wherein the delivering of oxygen comprises delivering at least one oxygen-containing compound that releases dissolved oxygen into cell culture.

57. The method of claim 53 wherein the delivering of oxygen is by means for delivery of oxygen is positioned upstream of input of circulating cell culture returning to the bioreactor.

58. The method of claim 50 or 53 further comprising stirring the cell culture or the culture medium or both the cell culture and the culture medium.

59. The method of claim 53 wherein the delivering of oxygen provides an average dissolved oxygen concentration of about 60%.

60. The method of claim 53 wherein the delivering of oxygen provides an average dissolved oxygen concentration of greater than about 40%.

61. The ^{method} apparatus of claim 60 wherein the delivering of oxygen provides an average dissolved oxygen concentration between about 30% and 90% or between about 40% and about 80% or between about 50% and 70%.

62. The method of claim 53 further comprising:
measuring physical and/or chemical parameter(s) of the cell culture and/or the culture medium.

63. The method of claim 62 wherein the measuring comprises measuring dissolved oxygen concentration.

64. The method of claim 62 wherein the measuring comprises measuring pH.

65. The method of claim 62 wherein the measuring comprises measuring temperature.

66. The method of claim 62 wherein the measuring comprises measuring pH and measuring dissolved oxygen concentration.

67. The method of claim 62 wherein the measuring comprises measuring cell density or amount of cells.

68. The method of claim 62 further comprising adjusting physical and/or chemical parameter(s) of the cell culture and/or the culture medium in response to data from the measuring.

69. The method of claim 68 wherein the adjusting comprises adjusting temperature to maintain a desired temperature.

70. The method of claim 68 wherein the adjusting comprises adjusting pH to maintain a desired pH.

71. The method of claim 68 wherein the adjusting comprises adjusting dissolved oxygen concentration to maintain a desired dissolved oxygen concentration.

72. The method of claim 68 wherein the adjusting comprises adjusting dissolved carbon dioxide concentration.

73. The method of claim 68 wherein the adjusting comprises adding a vector in response to a cell density or cell amount measurement

74. The method of claim 66 further comprising adjusting physical and/or chemical parameter(s) of the cell culture and/or the culture medium in response to data from the measuring.

75. The method of claim 74 wherein the adjusting comprises adjusting temperature to maintain a desired temperature.

76. The method of claim 75 wherein the adjusting comprises adjusting pH to maintain a desired pH.

77. The method of claim 75 wherein the adjusting comprises adjusting dissolved oxygen concentration to maintain a desired dissolved oxygen concentration.

78. The method of claim 75 wherein the adjusting comprises adjusting dissolved carbon dioxide concentration.

79. The method of claim 75 wherein the adjusting comprises adjusting dissolved oxygen concentration and adjusting dissolved carbon dioxide concentration, whereby in response to pH measurement(s), dissolved carbon dioxide levels are adjusted.

80. The method of claim 79 wherein the adjusting includes adjusting dissolved oxygen levels in response to dissolved oxygen measurement(s).

81. The method of claim 80 wherein the adjusting comprises adjusting pH to a desired level in response to pH measurement(s) by adjusting the dissolved carbon dioxide concentration such that dissolved carbon dioxide concentration is adjusted when pH varies from the desired level, and the dissolved oxygen measurement varies periodically as a function of time.

82. The method of claim 81 wherein the adjusting includes adjusting the dissolved oxygen concentration so that the dissolved oxygen measurement varies from 30% to 90% or from 40% to 80% or from 50% to 70%; or, so that the dissolved oxygen measurement averages about 60%.

83. The method of claim 82 wherein the adjusting includes adjusting the dissolved oxygen concentration so that the dissolved oxygen measurement varies from high value to low value over about 10 to about 30 minutes or over about 20 minutes.

84. The method of claim 81 wherein a plot of the dissolved oxygen measurement as a function of time comprises a sin wave.

85. The method of any one of claims 43, 50, 62, 68, 79 or 82-84, further comprising collecting the cells.

86. The method of any one of claims 43, 50, 62, 68, 79 or 82-84 wherein the cells contain a vector for replication of the vector and/or expression of exogenous nucleic acid molecules.

87. The method of claim 86 wherein the vector comprises a virus or a recombinant virus.

88. The method of claim 87 wherein the vector comprises a recombinant baculovirus.

89. The method of claim 87 further comprising collecting expressed product, and/or baculovirus and/or the cells.

90. Expressed product from the method of 89.

91. A method, for producing an expression product from a recombinant vector infected or transfected or inserted into a cell, or for producing a vector infected or transfected or inserted into a cell, comprising performing the method of any one of claims 43, 50, 62, 68, 79 or 82-84, wherein cells of the cell culture are infected or transfected with or have inserted into them the recombinant vector, or the vector, either prior to or during the method.

92. The method of claim 91 wherein the recombinant vector is a recombinant baculovirus and the cells are insect cells.

93. The method of claim 92 wherein the cells are infected during the method.

94. The method of claim 91 further comprising collecting the cells or the expression product or the recombinant vector or the vector.

95. The method of claim 91 wherein the cells are CHO cells.

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